Neuropathic Pain, Pain control system,
Sensory cortex and Sensory lesions

By

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By the end of this lecture the student will be able to:

1. Describe neuropathic pain
2. Explain the endogenous control of pain sensations
3. Describe stress analgesia
4. List the somatosensory areas of the cortex
5. Describe the organization, body presentation and functions of each one
6. Explain the consequences of their lesions
7. Explain the pathophysiology of different sensory lesions as syringomyelia, herpes zoster, peripheral neuropathy and sensory ataxia

Neuropathic pain

- Neuropathic pain is a chronic pain.
- Occurs when nerve fibers are injured.
- It is excruciating, and it is a difficult condition to treat.
- The resulting pain lasts much longer than the injury itself.
- The pain is often accompanied by **hyperalgesia** and **allodynia.**

- **Hyperalgesia** is an exaggerated response to a noxious stimulus.
- **Allodynia** is a sensation of pain in response to a normally innocuous stimulus. An example is the painful sensation from a warm shower when the skin is damaged by sunburn. Hyperalgesia and allodynia signify increased sensitivity of nociceptive afferent fibers.

- Examples for neuropathic pain: post herpetic (post-shingles) neuralgia, phantom limb pain, entrapment neuropathy (e.g. carpal tunnel syndrome), reflex sympathetic dystrophy/ causalgia (a spontaneous burning pain occurs long after trivial nerve trauma), and peripheral neuropathy

Pain modulation (modification)

Exaggeration (Facilitation); pathological e.g. cutaneous hyperalgesia and thalamic syndrome.
Inhibition (Suppression); physiological in pain analgesia system

Pain analgesia system

Spinal control= peripheral control (Gate theory)
Supraspinal control= central control (Descending pathways)

Spinal control= peripheral control (Gate theory):

Theory: there are many relay stations (synapses) in the sensory pathway of pain that act as a gate to be open or close.
Gates: 3

1. **Spinal gate** (substantia gelatinosa of relandi = SGR) = site of relay of 1st order neuron.
2. **Thalamic gate** (between PVLNT and nonspecific thalamic nuclei) = site of relay of 2nd order neuron.
3. **Reticular gate** (reticular formation) = site of relay of 2nd order neuron.

Spinal gate: At SGR, pain transmission can be blocked by:

1. **Collaterals from thick myelinated Aβ fibers of dorsal column tract:** stimulation of these sensory fibers by tactile stimuli (rubbing the skin, applying liniments near painful area).
2. **Collaterals from Aδ fibers of spinothalamic tract:** stimulation of these sensory fibers by counterirritant or acupuncture.
3. **Descending fibers (corticofugal or centrifugal or centripetal):** stimulation of these fibers by psychogenic excitation of central analgesia system.

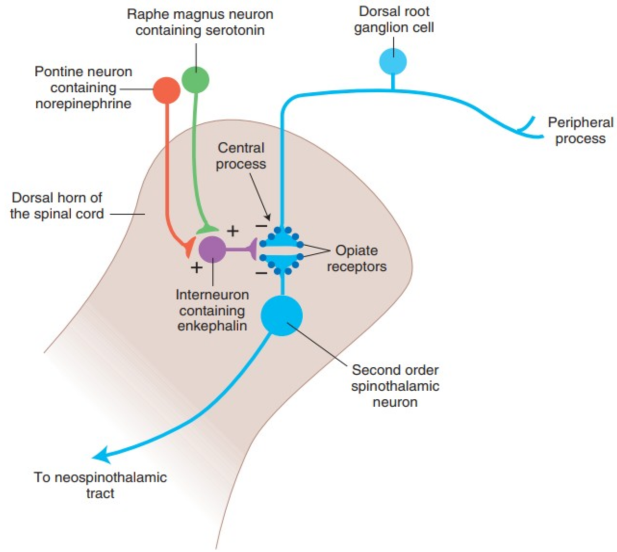
   N.B.:
   - **All act by presynaptic inhibition (GABA or Enkephalin)**
   - **Thalamic and reticular gates can be blocked by centrifugal fibers**

Supraspinal control= central control (Descending pathway):

Pain sensation is modulated by the following descending pathway:

Periaqueductal Gray Matter (PAG): The ***enkephalinergic*** neurons located in the periaqueductal gray matter of the *midbrain* project to the raphe magnus nucleus, which is located in the *medulla*.

Raphe Magnus Nucleus (RMN): The raphe magnus nucleus neurons are ***serotonergic***. The axons of these neurons descend to all levels of the spinal cord. ***Locus Ceruleus:*** Axons of noradrenergic locus ceruleus neurons located in the upper pons descend to the dorsal horn of the spinal cord. Both pathways synapse on interneurons located in the dorsal horn.



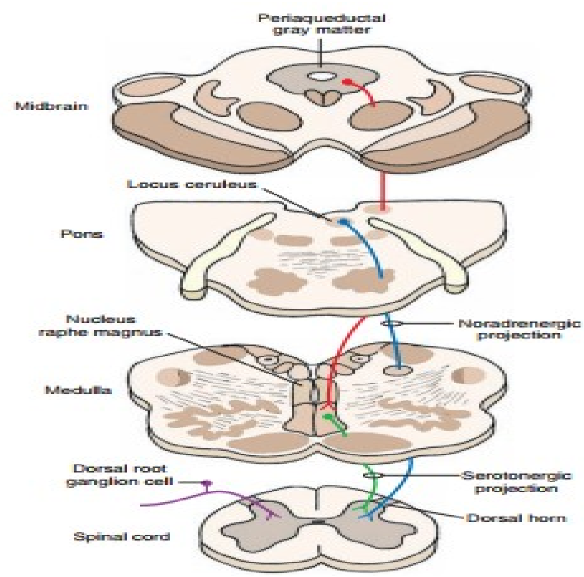
Descending pathways modulating pain sensory mechanism

Pain Inhibitory Complex (PIC): The ***enkephalinergic*** interneurons form axo-axonal type synapses on the 1st order (afferent) terminals of pain fibers and axo-dendritic type synapses on the 2nd order (dorsal horn) neurons mediating the pain sensation. Stimulation of the descending serotonergic projections from the raphe magus excites enkephalinergic interneurons in the spinal cord. Enkephalins released from these interneurons inhibit the release of transmitter from the central processes of nociceptive dorsal root ganglion neurons. Stimulation of the enkephalinergic interneurons also inhibits the second-order spinothalamic dorsal horn neurons via a postsynaptic mechanism.

N.B.: Electrical stimulation of PAG and RMN in human subjects and experimental animals is known to suppress the activity of nociceptive mechanisms (i.e., analgesia is produced).

N.B.:

Neurotransmitters Involved in Pain Pathways. The neurotransmitters released in the dorsal horn of the spinal cord, at the terminals of central processes of first-order nociceptive neurons (located in dorsal root ganglia), are believed to be **glutamate** and **substance P**. These neurotransmitters excite (**depolarize**) second-order spinothalamic dorsal horn neurons. The axons of these



second-order neurons cross to the contralateral side and form the ascending neospinothalamic tract.

Opiate receptors are present on the terminals of the central processes of the first-order nociceptive dorsal root ganglion neurons (presynaptic opiate receptors) and on the dendrites of second-order spinothalamic neurons (postsynaptic opiate receptors). The enkephalinergic interneurons located in the dorsal horn make axo-axonal and axo-dendritic synapses at the terminals of the central processes of the first-order nociceptive dorsal root ganglion neurons and dendrites of second-order spinothalamic neurons, respectively. The enkephalinergic interneurons are activated by the projections from the medullary serotonin-containing nucleus raphe magnus and pontine locus ceruleus noradrenergic neurons. Enkephalin released from terminals of enkephalinergic dorsal horn interneurons acts on the opiate receptors located on the central processes of the nociceptive neurons located in the dorsal root ganglia, reduces Ca^{2+} entry into the terminal (**presynaptic inhibition**), and decreases the release of neurotransmitters (glutamate and/or substance P). Enkephalin released from terminals of these dorsal horn interneurons also activates postsynaptic opiate receptors on the dendrites of the second-order spinothalamic neurons, **hyperpolarizes** them by increasing K^+ conductance, and inhibits them (**postsynaptic inhibition**). These actions of enkephalin attenuate the effects of nociceptive stimuli. Thus, stimulation of descending serotonergic and noradrenergic projections to the dorsal horn results in the stimulation of enkephalinergic interneurons in the dorsal horn, and enkephalin released from them inhibits second-order spinothalamic neurons by presynaptic and postsynaptic mechanisms.

The inhibitory effect of enkephalins are mediated by affecting K^+, Ca^{2+} flux. By binding to its receptors, dissociation of Gα and Gβγ subunits. The Gα directly interact with inward rectifying potassium channels causing hyperpolarization. The Gα also inhibits adenylate cyclase activity, which decrease the formation of cAMP, thus reducing the cAMP-dependent calcium influx. The Gβγ further reduces calcium influx by directly binding to various classes of Ca^{2+} channels.

N.B. Morphine injection is used to relieve pain by acting on its receptors in the pain analgesia system.

STRESS- ANALGESIA

It is well known that soldiers wounded in the battle often feel no pain until the battle is over. This is an example of **stress-induced analgesia** that can also be exemplified by reduced pain sensitivity when being attacked by a predator or other stressful events.

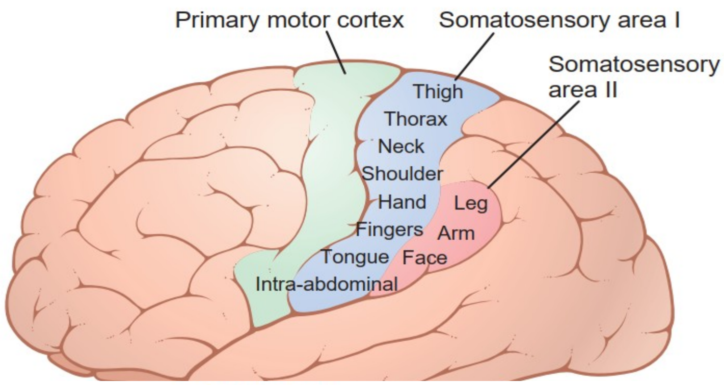
1. Impulses from cerebral cortex (limbic lobe) and hypothalamus (periventricular nucleus; PVN): fibers releasing endorphin to stimulate the PAG.
2. β-endorphin released in blood from anterior pituitary.

ACUPUNCTURE- ANALGESIA

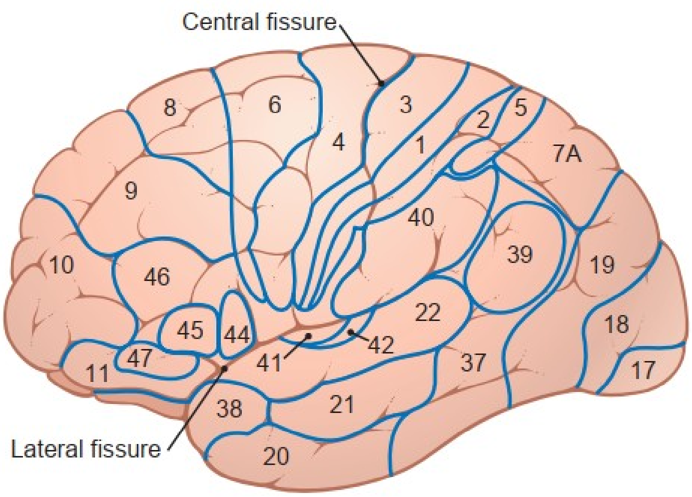
Acupuncture relieves pain by:

1. activation of spinal pathway of pain inhibition through activation of Aδ fibers.
2. psychogenic excitation of cerebral analgesia system.

Cerebral CORTEX



Brodmann's areas



The human cerebral cortex is divided into about 50 distinct areas called **Brodmann's areas** based on histological structural differences. Divided into:

Sensory cortex: receive

a. Somatic sensory signals terminate in the parietal lobe posterior to the central fissure.
b. Visual signals terminate in the occipital lobe.
c. Auditory signals terminate in the temporal lobe.

Motor cortex: the portion of the cerebral cortex anterior to the central fissure and constituting the posterior half of the frontal that control the muscle contractions and body movements.

Non sensory non motor (integrative) cortex: other cortical areas concerned with higher brain function e.g. intelligence, memory and speech.

SOMATOSENSORY CORTEX

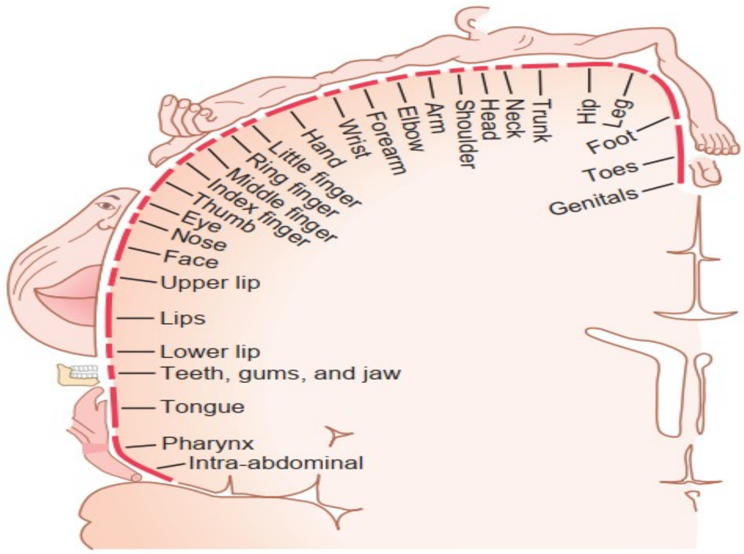
Somatosensory Areas I and II

Include:

- Somatosensory area I (1,2,3)
- Somatosensory area II (40)
- Somatosensory association area (5,7)

Spatial Orientation of Signals from Different Parts of the Body in Somatosensory Area I.

- Somatosensory area I lies immediately behind the central fissure, located in the postcentral gyrus of the human cerebral cortex (in Brodmann's areas 1, 2, and 3).
- Receives sensory information almost exclusively from the opposite side of the body (**Crossed**).
- Some areas of the body are represented by large areas in the somatic cortex—the lips the greatest of all, followed by the face and thumb—whereas the trunk and lower part of the body are represented by relatively small areas. The sizes of these areas are directly proportional to the number of specialized sensory receptors in each respective peripheral area of the body.
- The head is represented in the most lateral portion of somatosensory area I, and the lower part of the body is represented medially (**Inverted**).



Representation of the different areas of the body in somatosensory area I of the cortex.

Somatosensory area II

- **Location:** immediately behind the lower part of somatosensory area II.
- **Brodmann's areas:** 40
- **Body representation:**
  - •The face is represented anteriorly, the arms centrally, and the legs posteriorly.
  - • Poor localization
- **Receive signals from:**
  - ✓ Brain stem from both sides of the body.
  - ✓ Somatosensory area I
  - ✓ Other sensory areas of the brain (visual and auditory areas).
- **Projections from somatosensory area I are required for function of somatosensory area II. However, removal of parts of somatosensory area II has no apparent effect on the response of neurons in somatosensory area I.**

SOMATOSENSORY ASSOCIATION AREAS

- Brodmann's areas 5 and 7 of the cerebral cortex, located in the parietal cortex behind somatosensory area I.
- Play important roles in deciphering deeper meanings of the sensory information in the somatosensory areas. Therefore, these areas are called *somatosensory association areas.* Electrical stimulation in a somatosensory association area can occasionally cause an awake person to experience a complex body sensation, sometimes even the "feeling" of an object such as a knife or a ball. Therefore, it seems clear that the somatosensory association area

combines information arriving from multiple points in the primary somatosensory area to decipher its meaning.

- It receives signals from:
  (1) somatosensory area I, (2) thalamus, (3) visual cortex, and (4) auditory cortex.

Effect of Somatosensory Area I Lesion

Widespread unilateral lesion of somatosensory area I causes loss of the following types of sensory judgment on the ***contralateral*** side of the body.

Loss of fine sensations:

1. The person is unable to localize discretely the different sensations. However, he or she can localize these sensations crudely, such as to a particular hand, to a major level of the body trunk, or to one of the legs.
2. The person is unable to judge critical degrees of pressure against the body.
3. The person is unable to judge the weights of objects.
4. The person is unable to judge shapes or forms of objects. This condition is called ***astereognosis.***
5. The person is unable to judge texture of materials because this type of judgment depends on highly critical sensations caused by movement of the fingers over the surface to be judged.

- *Note that in the list nothing has been said about loss of pain and temperature sense. In the specific absence of only somatosensory area I, appreciation of these sensory modalities is still preserved both in quality and intensity. However, the sensations are poorly localized, indicating that pain and temperature localization depend greatly on the topographical map of the body in somatosensory area I to localize the source.*

Effect of the Somatosensory Association Area Lesion.

1. Loss of the ability to recognize complex objects felt by the opposite side of the body.
2. Loss of most of the sense of form of his or her own body or body parts on the opposite side. In fact, the person is mainly forgetting the opposite side of the body. Therefore, the person also often forgets to use the other side for motor functions as well. Likewise, when feeling objects, the person tends to recognize only one side of the object and forgets that the other side even exists. This complex sensory deficit is called ***amorphosynthesis***.

Sensory Lesions

(DISEASES ASSOCIATED WITH SENSORY DISTURBANCES)

SYRINGOMYELIA

- Congenital in origin.
- Slowly progressive disease.
- Manifestations start to appear at middle ages.
- Affecting mainly females.
- There is an abnormal overgrowth of neuroglial tissue (= gliosis) associated with cavitation around the central canal of the spinal cord.
- Affect lower cervical, upper thoracic region of spinal cord.
- The lesion may extend upwards in the brain stem, resulting in syringobulbia.

Manifestations:

(1) **Dissociated sensory loss** (= loss or some sensations and preservation or others). Because the lesion damages the crossing fibers of the lateral spinothalamic tracts in front of the central canal, there is *bilateral loss of pain and temperature sensations at the level of the lesion.* On the other hand. fine tactile and proprioceptive sensations are preserved because the *dorsal columns are not affected.* The lesion usually affects the *lower cervical and upper thoracic segments* of' the spinal cord, so its manifestations often have a *"jacket distribution".*

(2) **Bilateral muscle paralysis at the level of the lesion** of the *lower motor neuron lesion type* may occur due to damage of the anterior horn cells.

(3) **Unilateral or bilateral Horner's syndrome** may occur due to damage of the lateral horn cells.

(4) **Weakness (or paralysis) of the lower limb muscles** may occur in severe cases due to injury of the pyramidal tracts.

(5) **In syringobulbia**, symptoms of paralysis of some cranial nerves appear e.g. dysphagia or tongue atrophy due to injury of 9,1 0 and 12 cranial nerves.

TABES DORSALIS

- Late stage of *neurosyphilis*
- Inflammation of the posterior (or dorsal) nerve roots
- Commonly *bilateral*
- *At lower thoracic or lumbosacral regions* of *the spinal cord.*
- Affect both males and females

Manifestations:
Early:

<u>(1) Attacks of severe lancinating sharp pain</u> due to irritation or the pain-conducting afferent nerve fibers by the inflammatory process.
<u>(2) Degeneration of the gracile and cuneate tracts</u> because their thick Aβ nerve fibers are affected by compression and no *regeneration occur because these fibers lack neurolemma.* This causes atrophy of the dorsal column of spinal cord (tabes = atrophy) and leads to:
1- Loss of the fine tactile sensations and the vibration sense.
2- Loss of the conscious proprioception (kinesthetic) sensation (i.e. the sense of position and movement) as well as the subconscious proprioception information to the cerebellum. This leads to incoordination of voluntary movements called sensory ataxia which is characterized by:
a- The patient walks at a broad base and finds difficulty in walking.
b- Equilibrium disturbances : On closing his eyes, the patient sways and may fall (e.g. during washing his face). This is called Romberg's sign, and is due to loss of the main mechanisms that maintain equilibrium (i.e. vision and the proprioceptive sensations).
c- Stamping gait : During walking, the patient raises his legs too high then drops them forcefully because he is unaware of their position.

Late:
<u>(1) Loss of all sensations</u> in the regions innervated by the affected dorsal nerve roots due to degeneration of the afferent neurons. *Slow pain remains intact* because the thin type *C* nerve fibers resist compression.
<u>(2) Loss of reflexes</u> mediated by the affectcd dorsal nerve root including
(a) *Superficial* reflexes e.g. the withdrawal reflex which results in skin injury and ulceration
(b) *Deep reflexes* e.g. the stretch reflex (which result in loss of muscle tone and tendon jerks
(c) *Visceral reflexes* e.g. micturition reflex (which results in urine retention with overflow).
<u>(3) At the terminal stage,</u> syphilis may damage *the **pretectal area** in the midbrain* leading to the Argyll-Robertson pupil.

POLYNEURITIS (PERIPHERAL NEURITIS)

- Also called polyneuropathy *or peripheral neuropathy.*
- It is characterized by widespread bilateral symmetrical degeneration of the peripheral nerves in the limbs (including both sensory and motor nerves), and some cranial nerves may also be affected.

Causes

I. Vitamin B deficiency, particularly vitamin B1 (thiamine).

2. Certain metabolic disturbances (e.g. diabetes mellitus).

3. Toxic causes whether endogenous (e.g. uremia) or exogenous (e.g. lead, mercury and arsenic poisoning).

4. Nerve infection by certain viruses or bacteria (e.g. leprosy and tetanus).

5. Some endocrine diseases (e.g. hyperthyroidism and acromegaly).

Manifestations

(I) **Sensory disturbances:** at first there is paraesthesia (sensation of pin pricking, burning, numbness or tingling) in the fingers and toes. Later, anesthesia occurs in the peripheral parts of the limbs. taking a glove and stocking distribution. The superficial and deep sensations are also lost, and the latter leads to sensory ataxia.

(2) **Motor disturbances:** Bilateral lower motor neuron lesion, mostly peripheral (in the lower limbs) and loss of the superficial and deep reflexes.

HERPES ZOSTER (SHINGLES)

- Virus infection
- Affecting dorsal root ganglia especially of the thoracic nerves
- Leads to severe segmental pain that circles halfway around the body with skin vesicular eruption (skin rash of small vesicles) at corresponding dermatomal areas.